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On the modelling of genetic mutations and immune system competition☆

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ABSTRACT

This paper deals with the modelling of genetic mutations, which occur in almost all cells of a living system. The mutated cells display different stages of cancer progression and are contrasted by the action of the immune system cells. This investigation can be of interest in the evolutionary dynamics of cellular systems since the selective pressure on the mutated cells exerted by the immune system is analyzed. The proposed mathematical model is developed by means of the tools of the kinetic theory of active particles. Numerical simulations, obtained considering different values of the parameters in the model, show different emerging behaviors that are typical of the cancer-immune system competition.

1. Introduction

The last fifty years have witnessed rapid advances in biological sciences, mostly due to the developments of Genetics and Immunology, starting from the seminal paper [1]. In particular, the completion of the human DNA decoding made possible – theoretically – to explain several aspects of complex biological phenomena at the molecular scale, and the consequent refining of the investigation techniques made available a big amount of data and observations. Many scientists suggest the need for a new approach, where the complexity of a biological system may become understandable in terms of a small number of underlying principles, by means of suitable simplifications and representations of the phenomena, see for instance [2].

Physicists and mathematicians have accepted, following the guidelines of the biologists, the challenge to construct mathematical models able to reproduce emerging behaviors and possibly, as typical of the explorative models, to show phenomena that are not fully observed experimentally. Different mathematical approaches have been proposed, related to the different representation scales (molecular, cellular, and tissue scale) at which the biological system is analyzed. Among others, cellular automata models, population dynamics, population dynamics with internal structures, statistical models, macroscopic models, each of them developed at a specific observation scales and with specific mathematical tools. The reader can find additional bibliography in the book [3], in the review papers [4–6].

Various problems in the life sciences have been recently modelled by means of the tools of the mathematical kinetic theory of active particles, briefly KTAP, that have been settled in a general mathematical framework [7]. KTAP is applied in this paper at the cellular scale to describe, by mathematical equations, the system classified in cell populations, which are grouped according to their functional behavior. The term *active particles* [8] denotes the population entities that are

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identified by their *microscopic state*, which includes a scalar variable, the *activity*, related to the functional behavior of the particles. The state of the overall system is then described by a set of distribution functions over the microscopic state of the interacting active particles, and the evolution of the system is determined by the microscopic interactions, which are ruled by a somehow organized behavior or strategy, [9,10]. This approach is coherent to some suggestions of Hartwell el al. [11]: *"[…] the notion of function or purpose differentiate biology from other natural sciences […]. What really distinguishes biology from physics are survival and reproduction, and the concomitant notion of function"*. A further important hint is offered by Nowak, [12], who suggests to overcome the traditional approach to cancer modelling in terms of growth by looking at evolution and mutations.

KTAP's methods have been applied since [13] to model cancer phenomena and cellular dynamics and the competition between tumor and immune cells as documented in the book [14] as well as in several papers, [15–21].

This paper deals with the modelling of genetic mutations, which result in the onset of tumor cells with different progression features, thus generating biological heterogeneity phenomena [22,23], contrasted by the action of the immune system [18,19,24–29]. This investigation can be of interest in the evolutionary dynamics of cellular systems and it focuses on the evolution of progression and heterogeneity of living systems, and specifically on cancer phenomena and immune competition: the selective pressure on the mutated cells exerted by the immune system is analyzed, while in the literature, different types of selective pressure acting on cancer cells are considered, as for instance those exerted by therapies [30], or by environmental conditions [31]. Unlike other mathematical approaches, by KTAP methods, it is possible to highlight the heterogeneity, which may arise in the evolution of some biological systems (as, for instance, the increasing malignancy of the mutated cells). This gives a deeper insight on tumorigenesis adding information on the evolution of phenotypes. The above cited publications take into account heterogeneity of cell phenotypes and progression, but not mutations that generate new cell populations. The novelty of this paper with respect to the existing literature consists in introducing this specific aspect of mutations and the possibility of modelling pathways to reach the stage of cancer cells, including the transition from normal to neoplastic cells that, related to Darwinian selection, can have a crucial role in the immune competition.

Mutations at a lower scale, due to a rapid adaptation to the environment, have been first applied in [32] focusing on virus mutations carried by vertebrates. This paper is based on a mathematical framework defined in [4]. Moreover, paper [33] shows how mutations play an important role in the evolution of fibrosis disease in the presence of the immune system.

In general, mathematical models can be divided into two main groups: *predictive models*, that have the ability of describing the evolution of the system and that involve parameters, which have been well identified by comparisons with empirical data; *explorative models*, whose aim consists in investigating the trend of the system corresponding to different parameters which are left free. The model proposed in this paper is "explorative" rather than "predictive", and its analysis is mainly concerned with identifying the cellular phenomena that characterize the system evolution, depicting, if possible, emerging behaviors which cannot be easily derived from the initial conditions.

In detail, the paper is organized in five more sections which follow this introduction. Section 2 introduces a short phenomenological description of the biological processes we are dealing with. Section 3 deals with a brief description of the methods of the mathematical kinetic theory of active particles, and develops the mathematical framework as a reference for the modelling process. Section 4 presents a mathematical model for a system of cells populations, which may shift into new populations of cells with progressing mutation, contrasted by the immune system. Section 5 deals with a computational analysis of the initial value problem generated by the application of the model to real system analysis. Numerical simulations are related to the increase of the mutation rate of the abnormal cells, and to the increase of the proliferation of the immune system cells. Section 6 focuses on the critical analysis of the mathematical approach, suggesting possible further refinements, to be regarded as a research perspective.

2. A phenomenological description

A multicellular organism is constituted of interacting cells that, organized in specialized tissues cooperate to ensure the life of the organism. The cell functions are controlled by the *genes*, variable-length sequences of the DNA contained in the cell nucleus. The complex of the genes rules the life of the whole individual, leading the cells to perform their specific role in a tissue, limiting the growth of the cell number, forcing them first to reproduce and then to die.

A *gene mutation* is a permanent change in the DNA sequence that makes up a gene. Gene mutations occur in two ways: they can be inherited from a parent (*hereditary* or *germline* mutations), or acquired during a person's lifetime (*acquired* or *somatic* mutations). The corruption of a genetic locus (a specific site along the length the DNA string) may occur because of physical or chemical exogenous agents, or, more usually, because of some mistake during DNA replication in the process of the cell reproduction (mitosis). Remembering that approximately 10^{16} mitoses occur during a normal human life span, it seems likely that every day everyone has to suffer some kind of genome alteration, despite the efficient processes of "check and repair" of the duplicated DNA, which are typical of the mammalian organisms.

Almost every tumor arises because of random DNA mutations, which corrupt the genes of a cell and alter the genetic regulatory circuits that control the cell functions. Therefore, normal cells evolve progressively through increasingly abnormal (dysplastic) states until the neoplasia. The formation of a tumor and its development, the so-called *tumor progression*, is a quite complex process that normally spreads over many years (ten or more). Luckily, not every genetic corruption leads to the genesis of tumor cells: many of them are indifferent to the normal cell life, many others make the genome of the mutated cell so unstable that the cell dies after a short time.

The number of genetic mutations that are required to justify tumorigenesis is very high, far beyond the number of genetic mutations which occur during normal human life. However, sometimes a random DNA mutation may provide a normal cell with a sort of *genomic instability*: even if it does not seem to provide an immediate benefit in terms of proliferation and survival, genomic instability greatly increases the speed of further genetic mutations and makes easier the acquisition of other characteristics. Even if not easily quantified, the acquired genomic instability should be considered as an "enabling characteristic" in tumorigenesis. Therefore a cell may incur into a crucial and specific alteration in one of its genes, which gives it a significant advantage with regard to survival and proliferation, and allows it and its descendent to quickly advance along the tumor progression. Only a small portion of hundreds of the alterations present in many neoplastic cells' genomes actually plays causal roles in the process of tumorigenesis: mutation of a small number of critical control genes seems to be the way to acquire neoplastic cell phenotype.

Human cancer cells share a set of common characteristics (the so called "*hallmarks of cancer*"), acquired on the way to full malignant state [2]:

(i) capability of providing their own growth signals, i.e. *autocrine signalling*;
(ii) resistance to growth-inhibitory signals;
(iii) capability to proliferate indefinitely;
(iv) capability of angiogenesis;
(v) capability of escaping apoptosis;
(vi) metastatic capability.

Each characteristic, which is reached through multistep procedures, may represent a distinct phase in the tumorigenesis. They are acquired in different ways and times from tumor to tumor (though hallmarks (i) and (ii) are generally reached first), and even a single genetic mutation may help in reaching more than one characteristic simultaneously. Completion of each step in tumor progression can be viewed as the successful reaching of one of the above attributes.

Generally, a tumor develops progressively, demonstrating different gradations of abnormality along the way from being benign to metastatic. A tumor generally arises from the genetic mutation of a single cell (the so-called *monoclonal cancer*), and, at the same time, descendant cells with different types of genetic mutations are present; thus the tumor tissue shows *genetic heterogeneity* of cells [23]. Between the two extremes of fully normal tissues and highly malignant tissues lies a broad spectrum of intermediate appearance, which we read as a statistical distribution of the cells' progression. The different gradations of abnormality may well reflect *cell populations* that are evolving progressively away from normal and toward greater degrees of aggressive and invasive behavior.

The human body rises several lines of defense to contrast the onset and progression of a tumor: some of them are specific to the cell lifecycle, as the monitoring of DNA duplication, other defenses are specific to the organization of tissues, as the protection of stem cells and their genome. Besides those defenses, the human body is protected against infectious agents by the immune system.

The *immune system* is a complex of different cells and molecules which provides a strong and effective defense against pathogenic agents. The cells of the immune system, globally called leukocytes or white blood cells, communicate via cell-to-cell contact or via chemical signals through specific secreted substances and cooperate in continuously monitoring the environment, detecting and attacking foreign infectious agents.

The question whether the immune system, which is specialized to detect and eliminate foreign agents, may also recognize as "foreign" tumor cells or more in general mutated cells, which are native to the body, has been a matter of discussions between biologists. Today, evidence is rapidly accumulating that the immune system contributes to the body multilayered defenses against tumors. The interested reader may find in [34] a complete and up-to date reference about the biology of cancer.

3. The underlying mathematical framework

This section deals with the development of a general mathematical framework, which constitutes a paradigm for the derivation of specific models. This framework is derived following the kinetic theory of active particles [7]. Specifically, in order to reduce the complexity of the system under consideration, the overall system is divided into different populations of particles, each of them characterized by a common biological function and constituted by particles with a heterogeneous microscopic state. If the system is constituted by n populations of interacting particles (called *active particles*), whose microscopic state is represented by the scalar variable $u \in \mathbb{R}^+ = [0, \infty[$ (called *activity*), the evolution of the i-th population, for $i \in \{1, 2, \ldots, n\}$, is described by the distribution function $f_i = f_i(t, u) : [0, T] \times \mathbb{R}^+ \to \mathbb{R}^+$ over the state u at the time t.

The evolution of each population is determined by the interactions which occur between particles within the same or different populations. The considered interactions are both conservative (the microscopic state of the particles is modified without changing their whole number) and non-conservative (the number of particles is changed as a result of proliferative/destructive events, including transition of population). Three different types of particles can be distinguished: *candidate*, *test*, and *field* particles. Candidate particles can acquire, in probability, the state of the test particles after an interaction with field particles, while test particles may loose their state after interactions.

Under suitable integrability assumptions on f_i, gross averaged quantities can be computed. For instance, the *local number density* of particles, belonging to the i-th population at the time t, is computed as follows:

$$n_i(t) = \int_0^\infty f_i(t, u)\, \mathrm{d}u. \tag{1}$$

The evolution equation of the distribution function f_i is obtained by the balance of particles in the elementary volume $[u, u + \mathrm{d}u]$ of the space of the microscopic states. Technical calculations, see [14], yield:

$$\partial_t f_i(t, u) = J_i[f](t, u) = C_i[f](t, u) + T_i[f](t, u) + N_i[f](t, u), \tag{2}$$

where the left hand side term models the flow, at the time t, into the elementary volume of the state space of the i-th population due to transport and interactions, while the terms in the right hand side of Eq. (2) have, for $i, j \in \{1, 2, \ldots, n\}$, the following meaning:

- $C_i[f](t, u)$ models the flow, at the time t, into the elementary volume of the state space of the i-th population due to conservative interactions, and it has the following form:

$$C_i[f](t, u) = \sum_{j=1}^{n} \eta_{ij} \int_0^\infty \int_0^\infty \mathscr{B}_{ij}(u_* \to u |\, u_*, u^*) f_i(t, u_*) f_j(t, u^*)\, \mathrm{d}u_*\, \mathrm{d}u^* - f_i(t, u) \sum_{j=1}^{n} \eta_{ij} \int_0^\infty f_j(t, u^*)\, \mathrm{d}u^*, \tag{3}$$

  where η_{ij}, here assumed as constant, is the encounter rate between the candidate particle, with state u_*, of the i-th population and the field particle, with state u^*, of the j-th population. The term $\mathscr{B}_{ij}(u_* \to u |\, u_*, u^*)$ denotes the probability density that a candidate particle, with state u_*, of the i-th population ends up into the state u of the test particle of the same population after the interaction with the field particle, with state u^*, of the j-th population. Moreover, it satisfies the following condition:

$$\int_0^\infty \mathscr{B}_{ij}(u_* \to u |\, u_*, u^*)\, \mathrm{d}u = 1, \quad \forall\, u_*, u^* \in \mathbb{R}^+. \tag{4}$$

- $T_i[f](t, u)$ models the net flow, at the time t, into the elementary volume of the state space of the i-th population due to proliferative interactions with transition of population. This term has the following form:

$$T_i[f](t, u) = \sum_{h=1}^{n} \sum_{k=1}^{n} \eta_{hk} \int_0^\infty \int_0^\infty \mu_{hk}^{i \neq h}(u_*, u^*; u) f_h(t, u_*) f_k(t, u^*)\, \mathrm{d}u_*\, \mathrm{d}u^*, \tag{5}$$

  where $\mu_{hk}^{i \neq h}(u_*, u^*; u)$ models the net proliferation of the candidate particle, with state u_*, of the h-th population and the field particle, with state u^*, of the k-th population, into the i-th population, due to interactions that occur with rate η_{hk}.
- $N_i[f](t, u)$ models the net flow, at the time t, into the elementary volume of the state space of the i-th population due to proliferative and destructive interactions without transition of population:

$$N_i[f](t, u) = f_i(t, u) \sum_{j=1}^{n} \eta_{ij} \int_0^\infty \mu_{ij}(u, u^*) f_j(t, u^*)\, \mathrm{d}u^*, \tag{6}$$

  where $\mu_{ij}(u, u^*)$ models net flux within the same population due to interactions of the test particle, with state u, of the i-th population and the field particle, with state u^*, of the j-th population, which occur with rate η_{ij}.

Substituting the previous expressions into Eq. (2), yields:

$$\begin{aligned} \partial_t f_i(t, u) = {} & \sum_{j=1}^{n} \eta_{ij} \int_0^\infty \int_0^\infty \mathscr{B}_{ij}(u_* \to u |\, u_*, u^*) f_i(t, u_*) f_j(t, u^*)\, \mathrm{d}u_*\, \mathrm{d}u^* - f_i(t, u) \sum_{j=1}^{n} \eta_{ij} \int_0^\infty f_j(t, u^*)\, \mathrm{d}u^* \\ & + \sum_{h=1}^{n} \sum_{k=1}^{n} \eta_{hk} \int_0^\infty \int_0^\infty \mu_{hk}^{i \neq h}(u_*, u^*; u) f_h(t, u_*) f_k(t, u^*)\, \mathrm{d}u_*\, \mathrm{d}u^* \\ & + f_i(t, u) \sum_{j=1}^{n} \eta_{ij} \int_0^\infty \mu_{ij}(u, u^*) f_j(t, u^*)\, \mathrm{d}u^*. \end{aligned} \tag{7}$$

The above framework is space homogeneous. The interested reader can find recent developments on the modelling of space dependent phenomena in [14,35]. Specific models are obtained by a detailed modelling of microscopic interactions generating well defined expressions of the terms η, $\mathscr{B}$, and μ.

4. The mathematical model

The derivation of a model means providing, by a suitable phenomenological interpretation, a mathematical description of the microscopic interactions among the selected populations, which will be transferred into the framework proposed in Section 3.

The complexity of the biological phenomena, as briefly summarized in Section 2, is hardly depicted through a single mathematical model. Thus, we need to focus our attention to specific phenomena. In particular, we focus on early stages of tumorigenesis and its competition with the immune system cells. Moreover, we develop some approximations in order to reduce complexity, considering the following biological assumptions:

(i) Even if the above defined hallmarks are acquired by malignant cells in a quite variable order during tumor progression, we shall assume that some of them are typical of a specific state (e.g. the metastatic competence is typical of neoplastic cells) while others are common to both pre-neoplastic and neoplastic cells.

(ii) Genetic corruption occurs during the cell's lifetime and mostly during mitosis in the process of DNA replication. We shall assume that random DNA corruptions affect, with a small probability, normal cells and mutated (both pre-neoplastic and neoplastic) cells. The *increase of progression* corresponds to these random genetic mutations that, due to a selective evolutionary process, generate more aggressive mutated cells. A crucial genetic modification, leading to the acquisition of some of the above hallmarks, corresponds to a *mutation* in population, i.e. a change of population.

Obviously, not all mutations give a selective advantage in terms of cell survival and/or reproduction. When the genetic mutation gives no significative advantage (or even a selective disadvantage), the affected cell is destined to die, as a result of the competition with the other cells or with the environment. Therefore, since these mutated cells are "neutral" (they do not play an active part in the system's evolution), we neglect them and we consider only advantageous mutations.

(iii) The progression is a "one-way-only" process, i.e. it goes in the direction of even greater genetic mutations.

(iv) The populations of mutated cells show at the same time cells with different levels of progression. We shall refer to this statistically distributed progression in the environment as *heterogeneity of progressing cells*.

(v) The immune system is able to recognize and attack the mutated cells. At least at early steps of tumorigenesis, mutated cells display specific antigens on their surfaces; if an immune cell with matching receptors encounters such a mutated cell, it is able to kill it.

(vi) The mutated cells show the increasing ability to hide themselves from the immune system (*immunoselection*), and, at late steps of progression, the ability of *immunosubversion*, thus inhibiting and poisoning the immune system.

(vii) Cells are considered as homogeneously distributed. The model focuses on the heterogeneity of cell mutations; therefore, cells' spatial position does not modify the system evolution, since we focus on DNA mutations and changing phenotypes in a local environment. For our purpose, interactions are relevant, while the distance of interacting cells is irrelevant.

(viii) The interactions between cells are normally mediated by complex intercellular mechanisms and multiple cell interactions may occur, anyhow we simplify this process and we model *local interactions* only.

4.1. Cell populations and their activity variable

The model is developed assuming that the multicellular system is constituted by four interacting populations of cells expressing a well-defined "biological function" represented by the variable u, according to a functional partition of the system [9]. In the case of mutated cells, the function may be related to the acquisition of the previous defined hallmarks and, in the case of the immune system cells, it may be related to the immune response as a whole.

The model is derived assuming that the system is constituted by the following interacting cell populations:

1. **Normal cells**. The activity variable u is the **differentiation** related to the age of the cells. The normal cells, with growing values of u, are subjected to the standard cell lifecycle. However, a normal cell may undergo a **mutation** which gives it a significant advantage with regard to survival and proliferation, and allows it and its descendant to quickly advance along the tumor progression. As a consequence of mutation the normal cells may generate cells in a new population that we call pre-neoplastic cells.
2. **Pre-neoplastic cells**. Alteration in gene expression and the degeneration and evolution of cells into different levels of malignancy is called **progression**. The activity variable u represents the progression. Increasing values of u indicate an increasing intensity of progression. Pre-neoplastic cells may have a mutation and may generate cells in a new population that we call neoplastic cells.
3. **Neoplastic** or **Cancer cells**. The activity variable u is again the **progression**. They are characterized by a relatively greater genetic instability and ability to proliferate with respect to the pre-neoplastic cells. Moreover, these cells are partially able to escape the monitoring of the immune system.
4. **Immune system cells**. The activity variable u is a magnitude of the **activation** and of the response of the immune system to foreign agents. These cells have the ability to contrast progressing cells, through recognition and destruction. It is assumed that when an immune system cell encounters a pre-neoplastic or a cancer cell, it is able to recognize and kill it.

In the sequel, when we refer to cells of Population 2 and 3 as a whole, we call them **mutated cells** since they are both originated from mutations of normal cells. The functional partition in four populations, unlike previous models developed with KTAP methods, see [4], allows to have a more precise and accurate model, and allows a more detailed insight into heterogeneity and mutation phenomena.

4.2. Assumptions and interactions modelling

Referring to the mathematical framework proposed in Section 3 by Eq. (7) and the previous defined populations, the derivation of an evolution equation for the distribution functions over the activity of the cells needs the modelling of the microscopic interactions between individuals of the various populations.

In the sequel, we discuss only interactions which have non trivial outputs, i.e. an effective change (either in the microscopic state or in the cells' number) occurs after the interaction. Thus biological phenomena corresponding to interactions that give trivial outputs are not to be taken into account, as for instance the physiological birth and death of cells.

Specifically, the following types of interactions are considered:

- **conservative interactions**, which modify the microscopic state of each interacting cell but not the size of the populations;
- **proliferative** and **destructive interactions**, which generate the birth and death of cells due to pair cell interactions;
- **population transition**, which describes the proliferation of cells in a new population with respect to the mother cell.

The mathematical model is derived under the following mathematical assumptions:

1. The distributions of the cells' populations is described by the functions $f_1(t, u)$ (normal cells), $f_2(t, u)$ (pre-neoplastic cells), $f_3(t, u)$ (neoplastic cells), and $f_4(t, u)$ (immune cells).

2. The number of normal cells is assumed to be constant, considering that the apoptosis number roughly balances the mitosis number (*homeostasis* of the normal system). Then, the distribution $f_1(t, u)$ of the normal population cells is assumed constant in time, namely:

$$f_1(t, u) = f_1(0, u) = f_{10}(u), \tag{8}$$

where f_{10} is a constant in time distribution. Thus, normal cells that die because of apoptosis or have a transition into another cell population, are replaced by new normal cells. Moreover, all cell populations are normalized with respect to the local number density of the first population:

$$n_{10} = \int_0^\infty f_{10}(u)\,\mathrm{d}u = 1, \tag{9}$$

which, due to the normalization, is equal to the unity. The normalized densities for the other populations $i = 2, 3, 4$ writes:

$$n_i(t) = \int_0^\infty f_i(t, u)\,\mathrm{d}u. \tag{10}$$

3. The system of cells is assumed to be homogeneously distributed in space. According to a mean field approximation, the encounter rate is assumed to be constant for all interacting pairs; with rescale of time, we set $\eta_{ij} = 1$ for all $i, j \in \{1, 2, 3, 4\}$.

4. The term $\mathscr{B}_{ij}$ related to the transition probability density is assumed to be defined by a delta Dirac function (deterministic output of a pair interaction) depending on the microscopic state of the interacting pairs:

$$\mathscr{B}_{ij}(u_* \to u |\, u_*, u^*) = \delta(u - m_{ij}(u_*, u^*)). \tag{11}$$

5. Proliferation and destruction terms are considered as net ones.

Under the above assumptions, the next step is the modelling of each type of interactions.

• Conservative Interactions.

It is assumed that mutated cells are the only cells subject to conservative interactions, therefore $C_1(t, u) = C_4(t, u) = 0$. The conservative terms $C_2(t, u)$ and $C_3(t, u)$ are derived under the assumptions that mutated cells of populations 2 and 3 have a tendency to increase their microscopic state with a certain rate, regulated by the interactions with the cells of the first population which act as a counter clock since they are assumed to be constant in time. Bearing in mind the biological assumptions reported at the beginning of this section, this evolution toward higher level of progression is called **self-progression**. Moreover, it is assumed that the self-progression of neoplastic cells is greater than the self-progression of a pre-neoplastic cells. Accordingly to Eq. (11), we define:

$$m_{ij}(u_*, u^*) = \begin{cases} u_* + \varepsilon\alpha_E & \text{if } j = 1 \text{ and } i = 2, \\ u_* + \alpha_E & \text{if } j = 1 \text{ and } i = 3, \\ u_* & \text{otherwise,} \end{cases} \tag{12}$$

where α_E is a positive parameter related to the progression rate toward progressing states of mutated cells of the third population, while $\varepsilon < 1$ is a scale parameter, which takes into account the weaker progression rate of the second population with respect to the third one. Straightforward calculations give the following non-zero conservative terms:

$$C_2[f](t,u) = f_2(t, u - \epsilon\alpha_E) - f_2(t,u), \tag{13}$$

$$C_3[f](t,u) = f_3(t, u - \alpha_E) - f_3(t,u). \tag{14}$$

• Non-Conservative Interactions without Transition of Population.

Proliferation of cells. It is assumed that mutated cells may proliferate (without transition of population) when they encounter the normal cells. This corresponds to the fact that cells, as all living objects, need feeding to survive and that a healthy tissue in the cell micro environment has a feeding ability. In particular, the proliferation rate of a neoplastic cell is greater than the proliferation rate of a pre-neoplastic cell. Indeed, the ability of retrieving nutriments may be related to the genetic properties and the aggressiveness of the cell, as for instance the "Epithelial to Mesenchymal Transition", [36]. Accordingly to the mechanisms of the immune response, the proliferation of immune cells occurs only if an immune cell has encountered a mutated cell. Accordingly, we define:

$$\mu_{ij}(u,u^*) = \begin{cases} \varepsilon\beta_A & \text{if } j = 1 \text{ and } i = 2, \\ \beta_A & \text{if } j = 1 \text{ and } i = 3, \\ \beta_I & \text{if } j \in \{2,3\} \text{ and } i = 4, \\ 0 & \text{otherwise,} \end{cases} \tag{15}$$

where β_A is a positive parameter corresponding to the maximum proliferation rate of a progressing cell, β_I is the proliferation term of the immune cells, and ε is the scale parameter. The non-zero proliferation terms thus read:

$$P_2[f](t,u) = \varepsilon\beta_A f_2(t,u), \tag{16}$$

$$P_3[f](t,u) = \beta_A f_3(t,u), \tag{17}$$

$$P_4[f](t,u) = \beta_I f_4(t,u)(n_2(t) + n_3(t)), \tag{18}$$

where n_2 and n_3 are the local density of the populations 2 and 3, respectively, see Eq. (10).

Destruction of cells. The action of immune system cells may lead to the destruction of mutated cells which can be regarded as the *immune surveillance* of mutation progression. Neoplastic cells are destroyed by immune cells with less magnitude of the pre-neoplastic cells.

Neoplastic cells with a high level of progression have the ability to inhibit or destroy immune cells (*immune suppression* or *immune-subversion*). We assume a destruction of the immune cells by neoplastic cells, since inhibited immune cells do not play a relevant role in the competition and may be equivalently assumed as eliminated. Accordingly, we define:

$$\mu_{ij}(u,u^*) = \begin{cases} -\delta_A & \text{if } j = 4 \text{ and } i = 2, \\ -\varepsilon\delta_A & \text{if } j = 4 \text{ and } i = 3, \\ -\delta_S u^* & \text{if } j = 3 \text{ and } i = 4, \\ 0 & \text{otherwise,} \end{cases} \tag{19}$$

where δ_A is a positive parameter which characterizes the destruction ability of the immune cells, δ_S is a positive parameter which characterizes the destruction of the immune cells. Thus, the non-zero destructive terms read:

$$D_2[f](t,u) = -\delta_A f_2(t,u) n_4(t), \tag{20}$$

$$D_3[f](t,u) = -\varepsilon\delta_A f_3(t,u) n_4(t), \tag{21}$$

$$D_4[f](t,u) = -\delta_S f_4(t,u) \int_0^\infty u^* f_3(t,u^*), \tag{22}$$

where $n_4(t)$, according to Eq. (10), is the local density of the immune system cells.

• Proliferative Interactions with Transition of Population.

It is assumed that proliferative interactions with transition of population may occur and, after the interaction, a new cell of the new population appears. In particular, it is assumed that normal cells can mutate and become pre-neoplastic cells. In turn, the cells can further mutate and become neoplastic cells. Moreover, the microscopic state of the candidate particles does not change during the transition. The time rate is regulated by interactions with cells of the first population. Accordingly, we define:

$$\mu^i_{hk}(u_*,u^*;u) = \begin{cases} \gamma_A\delta(u - u_*) & \text{if } h \in \{1,2\}, k = 1, \text{and } i = h+1 \\ 0 & \text{otherwise,} \end{cases} \tag{23}$$

where γ_A is the jump rate of the population. Thus, the non-zero terms read:

$$T_2[f](t,u) = \gamma_A f_1(t,u), \tag{24}$$

$$T_3[f](t,u) = \gamma_A f_2(t,u). \tag{25}$$

Table 1
Populations, biological phenomena, and related parameters.

Cell populations	Biological phenomenon	Parameter
Normal cells	Mutation	γ_A
Pre-neoplastic cells	Self-progression	$\varepsilon\alpha_E$
	Proliferation	$\varepsilon\beta_A$
	Mutation	γ_A
Neoplastic cells	Self-progression	α_E
	Proliferation	β_A
	Immune subversion	δ_S
Immune system cells	Proliferation	β_I
	Destruction of pre-neoplastic cells	$-\delta_A$
	Destruction of neoplastic cells	$-\varepsilon\delta_A$

4.3. The equations of the model

Replacing the previous terms into Eq. (7), and recalling that the normalization is such that $n_1(t) = n_{10} = 1$, yields:

$$\begin{cases} \partial_t f_1 = 0, \\ \partial_t f_2 = \left(\varepsilon\beta_A - \delta_A \displaystyle\int_0^\infty f_4(t,u^*)\mathrm{d}u^* - \gamma_A - 1\right) f_2(t,u) + \gamma_A f_1(t,u) + f_2(t,u-\epsilon\alpha_E), \\ \partial_t f_3 = \left(\beta_A - \varepsilon\delta_A \displaystyle\int_0^\infty f_4(t,u^*)\mathrm{d}u^* - 1\right) f_3(t,u) + \gamma_A f_2(t,u) + f_3(t,u-\alpha_E), \\ \partial_t f_4 = \left(\beta_I \displaystyle\int_0^\infty f_2(t,u^*)\mathrm{d}u^* + \beta_I \int_0^\infty f_3(t,u^*)\mathrm{d}u^* - \delta_S \int_0^\infty u^* f_3(t,u^*)\mathrm{d}u^*\right) f_4(t,u). \end{cases} \tag{26}$$

The above model is nonlinear, with quadratic type nonlinearity and it is characterized by 7 phenomenological parameters: the α parameters are related to mass conservative encounters, the β, δ and γ parameters are related to proliferating/destructive encounters, and ε is a scale parameter. All parameters are positive quantities (eventually equal to zero). Practical values of these parameters are small with respect to unity.

Particularly important is the fact that the parameters characterizing the model have a well defined biological meaning. Therefore, the computational analysis can be technically addressed to analyze how different values of the biological functions may be inserted into the model to describe phenomena of interest in biological sciences.

The Table 1 summarizes the cells' populations, the biological phenomena taken into account and the related mathematical parameters concerning the model.

The evolution equations for the density $n_i(t)$, for $i \in \{1, 2, 3, 4\}$, are obtained from Eqs. (26) by integration on $\mathbb{R}^+$:

$$\begin{cases} \partial_t n_1(t) = 0, \\ \partial_t n_2(t) = (\varepsilon\beta_A - \delta_A n_4(t) - \gamma_A) n_2(t) + \gamma_A + \displaystyle\int_{-\epsilon\alpha_E}^0 f_2(t,u)\,\mathrm{d}u, \\ \partial_t n_3(t) = (\beta_A - \varepsilon\delta_A n_4(t)) n_3(t) + \gamma_A n_2(t) + \displaystyle\int_{-\alpha_E}^0 f_3(t,u)\,\mathrm{d}u, \\ \partial_t n_4(t) = (\beta_I n_2(t) + \beta_I n_3(t) - \delta_S a_3(t)) n_4(t). \end{cases} \tag{27}$$

This system is not in a closed form, since the distribution functions $f_i(t,u)$, for $i \in \{1, 2, 3, 4\}$, are unknown.

5. Simulations and analysis of the model

Simulations can be obtained by solving the mathematical problem stated by linking the Eqs. (26) to suitable initial conditions. The statement of the initial value problem can be formally written as follows:

$$\begin{cases} \partial_t \mathbf{f}(t,u) = \mathbf{J}[\mathbf{f}](t,u), \\ \mathbf{f}(t=0,u) = \mathbf{f}_0(u), \end{cases} \tag{28}$$

where $\mathbf{f} = (f_1, f_2, f_3, f_4)$ and $\mathbf{J}$ represents the right hand side terms of the system of Eq. (26). The initial condition $\mathbf{f}_0 = (f_{10}, f_{20}, f_{30}, f_{40})$ is such that, due to normalization, all distribution functions are divided by the number of cells in the first population that is assumed to be constant in time:

$$f_{10} = f_{10}(u), \quad n_{10} = 1, \tag{29}$$

while $f_{20} = f_{30} = 0$. The initial distribution of immune system cells, f_{40}, is different from zero corresponding to the sentinel value of the immune system.

We are interested in studying both the time evolution of the number densities n_i, with $i = 1, 2, 3, 4$, which indicates cells in a certain population, and the time evolution of the distribution functions f_i, with $i = 1, 2, 3, 4$, which indicates the progression within each functional subsystem. However (27) is not closed and it has to be integrated jointly with (26).

The initial value problem for a class similar to (26) has been studied in [14], where estimates on the system of the number densities have been used to compute bounds on the system of the distribution functions so that a local existence theorem has been extended, in some particular cases, to large times.

This topic is not treated here, where the mathematical problems induce additional difficulties related to the larger number of equations, while this paper is devoted to simulations to investigate the predictive ability of the model.

Computations are obtained exploiting the same methods of [14], namely by collocation and interpolation functions of the distribution function, so that the problem for a system of integro–differential equations is approximated by a problem for a system of ordinary differential equations. Sinc functions [37,38] can be used for interpolation in assuming the natural trend to zero at infinity.

Simulations are addressed to show the onset of genetic mutated cells, the development of heterogeneity, and the competition among mutated cells and cells of the immune system. In particular, as objectives of the computational analysis, we focus on the following two aspects, among various conceivable ones:

- *The sensitivity analysis of the rate of mutation* γ_A.
- *The sensitivity analysis of the immune system activation* β_I.

In view of this, we assume that six of the seven parameters of the model are fixed, while one of them, the free parameter, spans from zero to higher values; for the first objective, we consider γ_A as the free parameter and for the second objective we choose β_I as the free parameter. Simulations should visualize how increasing values of the free parameter modify the overall evolution of the system, with special attention to progression and heterogeneity phenomena.

Each simulation is performed choosing a non-zero initial condition only for $f_1(0, u)$ and $f_4(0, u)$, which is a choice coherent to a physiological state, where only normal cells and immune system cells are initially present.

The common parameters proposed for all the set of simulations are $\alpha_E = 0.5$, $\beta_A = 0.2$, $\delta_A = 0.3$, $\delta_S = 0.01$, $\varepsilon = 0.1$, corresponding to: a not negligible effect of the progression (α_E), a low proliferation of the mutated cells (β_A), a low level of immune subversion (δ_A), a not too aggressive response of the immune system (δ_S).

The scale parameter (ε) is related to the difference of behaviors between neoplastic cells and pre-neoplastic cells. The magnitude of the parameters β_I and γ_A is specified in the following subsections.

5.1. Sensitivity analysis of the mutation rate γ_A

As a first step we consider the onset of mutated cells and their competition with the immune system cells for different values of the mutation rate γ_A. Specifically, fixing the parameters of the model as indicated above, we set $\beta_I = 0.3$, which corresponds to a weak immune system cell proliferation, and let γ_A vary. It is expected that increasing values of γ_A generate increasing manifestation of progression and heterogeneity phenomena.

For *low mutation rate* ($\gamma_A = 0.11$), see left panel of Fig. 1, the number density of neoplastic cells is increased less than the number of the pre-neoplastic. Indeed, it is assumed that neoplastic cells have a greater rate of progression with respect to the pre-neoplastic ones but their number and consequently their proliferation depends on how many pre-neoplastic cells effect the transition of population. In the right panel of Fig. 1, we show the distribution function of the populations 2 and 3 at different instants of time. The role of the conservative interactions that shift the populations 2 and 3 toward increasing values of progression is very evident.

If we stretch out the time simulation, a critical change in the behavior of the competition occurs, and it is possible to identify two times t_2^c and t_3^c after which the number of pre-neoplastic and neoplastic cells respectively starts to decrease, see the left panel of Fig. 3, and Fig. 2 for their distribution functions, until the control and the partial depletion.

Increasing values of γ_A do not change the asymptotic (in time) scenario since the immune system is still able to react and proliferate in response to mutated cells. The main difference is that the effect of the mutations with population transition is greater, see Fig. 4 (with respect to the right panel of Fig. 1), and the critical time t_4^c necessary for the immune system cells to be able to contrast neoplastic cells is greater than in the case of low values of γ_A (see Fig. 3). Of course this time depends not only on the specific choice of all parameters but also on the initial conditions.

The previous results suggest that when the rate of mutation γ_A increases, the time t_2^c, t_3^c from which the immune system cells start killing the mutated cells is a decreasing function of γ_A. Fig. 5 is realized considering five different rates of mutation 0.11, 0.22, 0.40, 0.65, 0.9. As shown, these simulations support our conjecture both for pre-neoplastic and neoplastic cells.

5.2. Sensitivity analysis of the proliferation rate β_I

In this subsection we vary the rate of proliferation β_I of the cells of the immune system. The parameters are chosen such that the proliferation of the mutated cells (β_A) and the effects of the self-progression (α_E) are not negligible and the rate of mutation γ_A is at an intermediate level. Specifically, fixing the parameters as mentioned in the previous section, we set $\gamma_A = 0.4$ and we vary β_I.

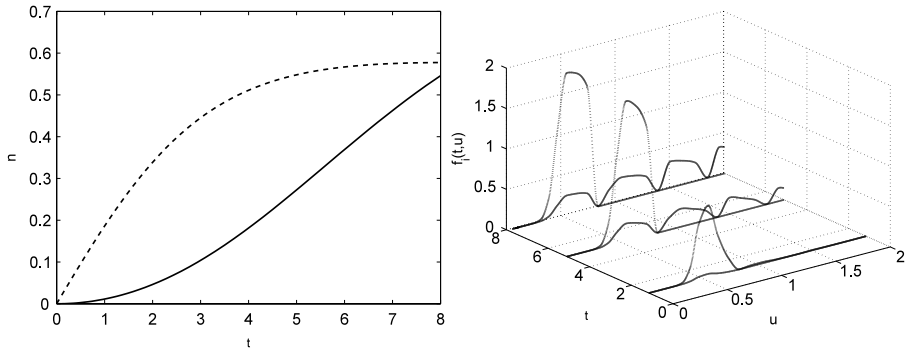

Fig. 1. The evolution in the time interval [0, 8] of the densities of pre-neoplastic cells (dotted line), neoplastic cells (continuous line) for $\gamma_A = 0.11$ (left panel). Distribution functions, for $\gamma_A = 0.11$, of the pre-neoplastic (dotted line) and the neoplastic cells (continuous line) at different times (right panel).

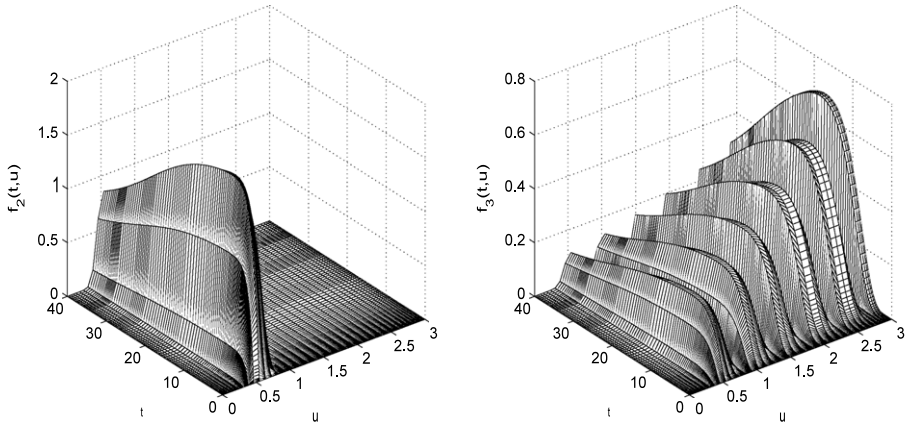

Fig. 2. Distribution functions of the mutated cells for longer times ($\gamma_A = 0.11$). Pre-neoplastic cells (left panel) and neoplastic cells (right panel).

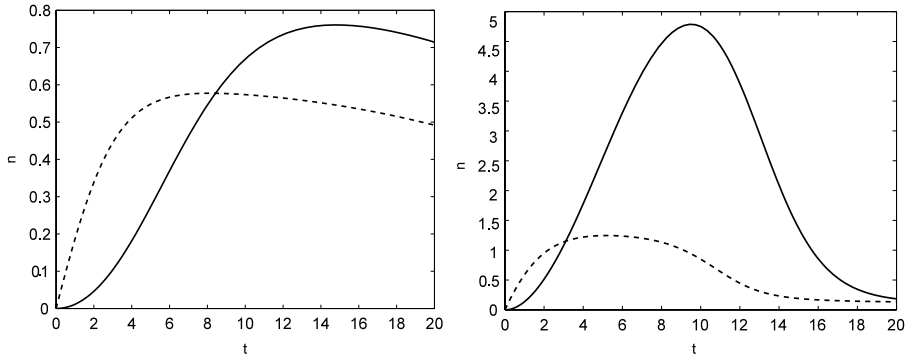

Fig. 3. Time evolution of the densities of pre-neoplastic cells (dotted line) and neoplastic cells (continuous line) in the time interval [0, 20] for $\gamma_A = 0.11$ (left panel) and for $\gamma_A = 0.4$ (right panel).

It is expected that increasing values of β_I produce an increasing activation of the immune system and consequently a more efficient destruction of the mutated cells in time.

If the *immune system cells do not proliferate* ($\beta_I = 0$), while mutated cells are able to proliferate, the number of pre-neoplastic cells increase in time slowly, while neoplastic cells proliferate indefinitely (see the left panel of Fig. 6). The immune system cells are unable to proliferate, thus the competition with mutated cells results in a reduction of the immune system cells (right panel of Fig. 6). This is the only case in which the immune system cells decay, asymptotically in time, to zero. The model, in this case, reproduces the progressive evolution of the mutated cells towards higher levels of mutation.

Letting an *intermediate proliferation value of the immune system cells* ($\beta_I = 0.55$), the competition with the mutated cells is evident. Indeed, as shown in the left panel of Fig. 7, the immune system cells are able to reduce the number of pre-neoplastic

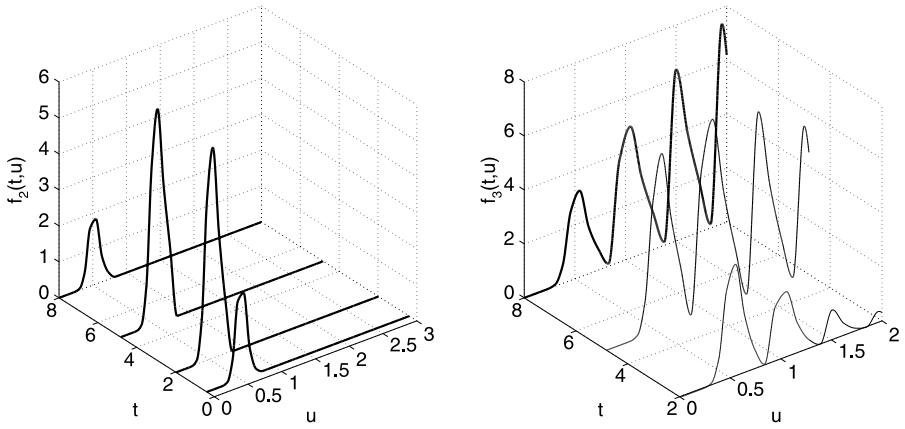

Fig. 4. Distribution functions of the pre-neoplastic cells (left panel) and the neoplastic cells (right panel) for $\gamma_A = 0.9$ at different times.

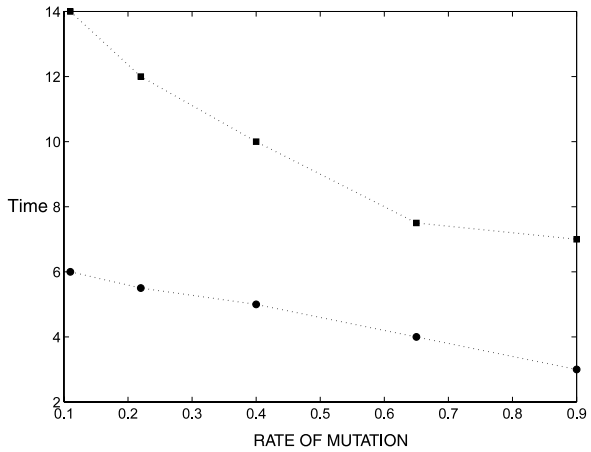

Fig. 5. Rate of mutation versus the time t_2^c and t_3^c from which the mutated cells, respectively pre-neoplastic (circle dot) and neoplastic (square dot) cells, start decreasing.

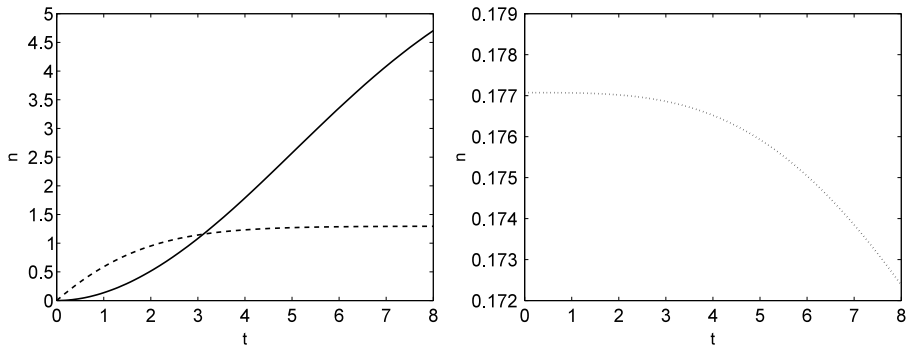

Fig. 6. Evolution in time of the densities of pre-neoplastic cells (dotted line) and neoplastic cells (continuous line) in the left panel, and immune system cells in the right panel, in the time interval [0, 8] for $\beta_I = 0$.

cells after a time t_2^c, while the number of neoplastic cells starts to decrease after a greater time $t_3^c > t_2^c$. Nevertheless the immune system cells, which keep growing in time, asymptotically are able to control and partially deplete mutated cells.

Increasing the value of β_I leads to a reduction in the critical times t_2^c and t_3^c but, as expected, the asymptotic scenario is unchanged, see Fig. 7. Moreover, immune system cells contrast more efficiently neoplastic cells with a low level of mutation u, as shown in Fig. 8, where the distribution functions at different times for two values of the activation rate β_I are reported.

The results of the simulations are summarized in the Table 2.

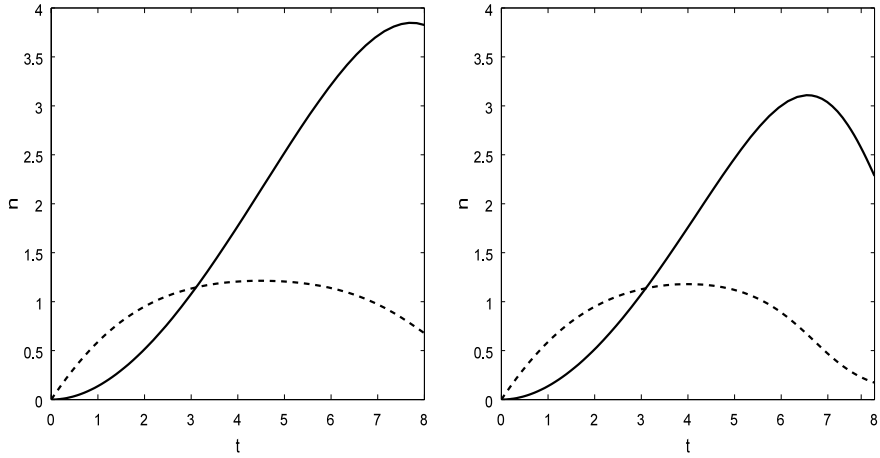

Fig. 7. Time evolution of the densities of pre-neoplastic cells (dotted line), neoplastic cells (continuous line) in the time interval [0, 8] for $\beta_I = 0.55$ (left panel) and for $\beta_I = 0.85$ (right panel).

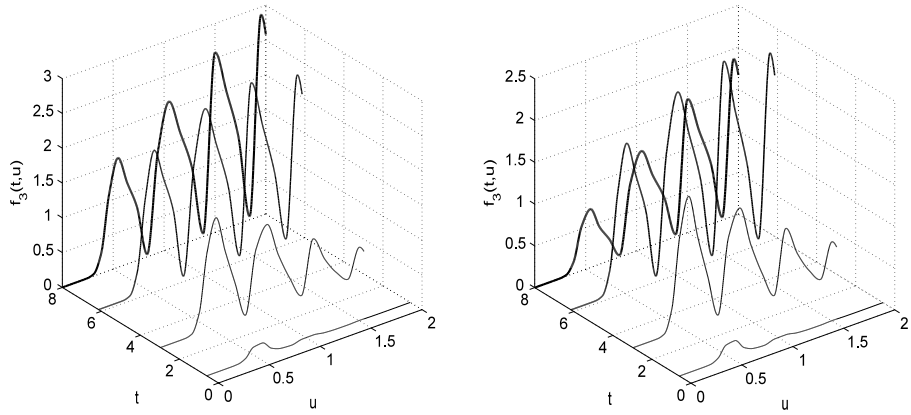

Fig. 8. Distribution function of the neoplastic cells at different times for $\beta_I = 0.55$ (left panel) and for $\beta_I = 0.85$ (right panel).

Table 2
Biological phenomena in the time interval [0, 20] for the case γ_A as free parameter and in the time interval [0, 8] for the case β_I as free parameter.

Fixed parameters	Free parameters	Biological results
		Onset of mutated cells
	$\gamma_A = 0.01$	Immune system cells low activation
$\varepsilon = 0.1$		Mutated cells destruction (slowly in time)
$\beta_A = 0.2$		Prevalence of neoplastic cells
$\delta_A = 0.3$	$\gamma_A = 0.4$	Immune system cells activation
$\beta_I = 0.3$		Mutated cells destruction (quickly in time)
$\delta_S = 0.01$		High heterogeneity of mutated cells
$\alpha_E = 0.5$	$\gamma_A = 0.9$	Immune system cells high activation
		More efficient (in time) destruction of mutated cells
		Immune system cells inhibition and immunosuppression
	$\beta_I = 0$	Mutated cells evolution in time
$\varepsilon = 0.1$		
$\beta_A = 0.2$		Non-negligible immune cells proliferation
$\delta_A = 0.3$	$\beta_I = 0.55$	Pre–neoplastic cells destruction
$\gamma_A = 0.4$		Neoplastic cells weak destruction
$\delta_S = 0.01$	$\beta_I = 0.85$	Immune system cells high proliferation
$\alpha_E = 0.5$		Efficient destruction of mutated cells

6. Critical analysis and perspectives

A mathematical model has been proposed to describe the onset of mutated cells and their progression towards higher values of mutations, contrasted by the immune system cells, when these cells have the ability to recognize and kill them. A mathematical structure has been derived according to the methods of the mathematical kinetic theory of active particles, and, subsequently, a specific model has been derived on the basis of a detailed mathematical description of interactions at the cellular scale. Simulations have shown how this model is able to predict interesting phenomena concerning heterogeneity and progression of the mutated cells. The validity of the model is strictly related to the reproducibility of emerging behaviors.

Further investigations may be developed on the role of the immune system. Our assumption is that the immune system, both with innate and adaptive response, can recognize and kill mutated cells. However, cancer cells are somehow invisible to the immune system (*tumor escape*) attack by the selection of non-immunogenic tumor cells (tumor cells which are tolerated by the immune system, a process called *immunoselection*) or by the active suppression of the immune response, the *immunosubversion* (this phenomenon is simulated in our model by the parameter δ_S).

Immune system cells are able to perform complex tasks such as learning, acquiring the capability of distinguishing between host entities (self) and foreign or infected entities (non-self), and evolving in time to achieve better results, retaining memory of previous encounters with foreign agents for a quicker response in case of re-infection and constantly updating their reactive potential.

The specificity of the mechanism receptor-antigen is quite efficient and allows a strong defense against a very large spectrum of possible infectious agents. The capability to detect an infectious agent is called the *expressed repertoire*, which is continuously updated by signals specific to the receptors of each lymphocyte: only those, which receive the survival signal by their environment survive, while the others are selected for apoptosis and are replaced by new lymphocytes with different receptors. This complex phenomenon can be viewed as an *evolutionary dynamic* leading to a *learning* of the immune system.

A further development, from a both mathematical and methodological point of view, can be developed by using the structures proposed in Section 3 to the molecular scale of representation (scale of genes, [39]). Specifically, the molecular scale refers to the evolution of a cell regulated by its genes. The output of the dynamics at the molecular scale determines the main biological functions of the cell. The aim is a *multiscale description* of the genetic instability, and the derivation, from genes expression, of the cellular functions. It is a challenging research perspective, where some interesting recent results have been given, among others [40–42], however this topic still needs to be developed. The link between the molecular and the cellular scale allows to derive the time evolution of models at the tissue scale obtained by asymptotic methods such as those used in [43] to derive the celebrated Keller–Segel model.

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